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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,922	GEISSMANN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/19/03, 12/10/02; 5/22/02* .

2a)☐ *This action is* **FINAL**. 2b)☒ *This action is non-final.*

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *3, 6-9, 11-15, and 17-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,10 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. *See 37 CFR 1.85(a).*

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received *in Application No.* _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12102002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-37 are pending.

2. Applicant's election with traverse of Group I, Claims 1-2, 4-5, 10 and 16 drawn to a method of modulating the immune system of an animal wherein the modulation is activation of an antigen-presenting cell using a specific retenoid and a specific cytokine wherein the retenoid is a pan-RXR agonist SR11237 and pharmaceutically acceptable salts, esters and prodrugs thereof that read on the cytokine species tumor necrosis factor, filed 5/19/03, is acknowledged. The traversal is on the grounds that (1) Groups I-XLVI are closely related in subject matter, as such a search of one group of claims is likely to encompass subject matter pertinent to the patentability of all groups since all Groups have been classified in Class 424 and subsclass 198.1. (2) Applicant submits that restricting the present application into more restriction groups than there are claims pending in the application is improper. Instead, the Examiner's grouping of claims would seem more appropriate for an Election of Species requirement under MPEP 809.02(a) although Applicants respectively assert that such as a requirement would also be improper. (3) The Examiner has not shown by appropriate explanation supporting a serious burden if restriction were not required. This is not found persuasive because of the reasons set forth in the restriction mailed 4/22/02. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group I and Groups II-XLVI is still deemed proper and is therefore made FINAL.

3. Claims 3, 6-9, 11-15, and 17-37 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-2, 4-5, 10 and 16 are being acted upon in this Office Action.

5. Claim 16 is objected for because said claim depends from non-elected claim 11.

6. The international report crossed out on PTO 1449 filed 1/9/01 has been considered but crossed out.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 4-5, 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII (page 15 of the specification), RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[l-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid, (2) a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or RARα antagonist BMS749 and an inflammatory cytokine, **does not** reasonably provide enablement for (1) a method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, (2) the method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, wherein the effect upon said antigen presenting cell is activation of said cell, (3) the method of "modulating" the immune system of any animal by affecting the physiology of *any* antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell wherein the retinoid is any pan-RXR agonist, and any RAR antagonist such as any "Compound V", "Compound II", "compound VIII", any pharmaceutical acceptable salts, esters, and prodrugs thereof, (4) the said method wherein the cytokine is any TNFα variants, any TNFα analogues, any TNFα derivatives, any IL-1β "variants", any IL-1β "analogues" and any IL-1β derivatives thereof, and (5) the said method wherein the antigen is any dendritic cell, or any Langerhans cell for the claimed method of

"modulating" the immune system of any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[1-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. However, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88). The specification on page 24 discloses that the antigen-presenting cells in the claimed methods may be any antigen-presenting cell, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and the like. The specification on page 29 defines the term "cytokine" as growth factors, interleukins, colony-stimulating factors, interferon and lymphokines, which

may be natural, synthetic, or Recombinant, analogues or homologues and TNFα analogues. The specification further defines "antigen-presenting cell" refers to any cell, regardless of the tissue derivation or source of the cell, that is involved in certain aspects of the immune response of an organism... Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and "the like".

The specification does not teach how to make *any* pan-RXR agonist, *any* RAR antagonist, any "Compound V", *any* "Compound II", *any* "Compound V", *any* "Compound VIII" and *any* ester and prodrug thereof, and *any* "analog", and *any* "derivatives" of TNFα or IL-1β for the claimed method of modulating immune system of animal for the following reasons. First, there is insufficient guidance as to the structure of *any* pan-RXR agonist, *any* RAR antagonist, *any* analog, and *any* derivatives of any TNFα and IL-1β because the term "agonist", "antagonist", "analog", "derivatives" and "compound" could be a polynucleotide, a polypeptide, or a small organic molecule. Given the indefinite number of undisclosed pan-RXR agonist, *any* RAR antagonist, *any* analog of any TNFα and IL-1β, and *any* derivatives of any TNFα and IL-1β, there is insufficient guidance as to the structure, much less about its function, in turn, would be useful for modulating the immune response of an animal wherein the modulating can be stimulatory or inhibitory.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al.*, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

Second, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88).

Third, not all retinol has been shown to enhance or decrease immune responses, depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. Further, the term "modulating" can be stimulatory or inhibitory; the stimulatory and inhibitory actions are mutually exclusive.

Geissmann *et al* teach that retinol is metabolized intracellularly via two distinct pathways forming its active derivatives (a) retinoic acids (RAs), all-transRA (tRA), and 9-cis RA (9cRA) whose effects are transduced by retinoid receptors (RARs α, β or γ) and retinoic X receptors (RXRs). Geissmann *et al* further teach that only selective retinoids binding to certain receptors are capable can activate the specific type of antigen presenting cell or capable of inducing apoptosis of certain type of antigen presenting cells such as immature dendritic cell (See entire document).

Given the indefinite number of undisclosed pan-RXR "agonist", RAR "antagonist", the diverse functions of each agonist, antagonist, analog and derivative of TNFα and IL-1β through distinct receptors pathways, it is unpredictable which one of said undisclosed pan-RXR "agonist", RAR "antagonist", TNFα and IL-1β "analog" and "derivatives" thereof would maintain the same structure and function, in turn, would be useful for modulating the immune system for treating any disease. Finally, Even if the claimed method is limited to the specific retinoids such as SR11237, there is no in vivo working example demonstrating that the claimed method is effective for modulating the immune system for treating any disease.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-2, 4-5, 10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, (2) the method of "modulating" the immune system of any animal by affecting the physiology of any antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell for treating *any* disease, wherein the effect upon said antigen presenting cell is activation of said cell, (3) the method of "modulating" the immune system of any animal by affecting the physiology of *any* antigen-presenting cell in said mammal, comprising contacting said antigen-presenting cell with an effective amount of at least one of *any* "retinoid", and *any* cytokine under conditions whereby the "physiology" of said antigen presenting cell wherein the retinoid is any pan-RXR agonist, and any RAR antagonist such as any "Compound V", "Compound II", "compound VIII", any pharmaceutical acceptable salts, esters, and prodrugs thereof, (4) the said method wherein the cytokine is any TNFα variants, any TNFα analogues, any TNFα derivatives, any IL-1β "variants", any IL-1β "analogues" and any IL-1β derivatives thereof, and (5) the said method wherein the antigen is any dendritic cell, or any Langerhans cell for the claimed method of "modulating" the immune system of any animal.

The specification discloses only a method of inhibiting retinol induced apoptosis of immature dendritic cells in vitro comprising contacting said dendritic cell with an effective amount of the specific retinol and an inflammatory cytokine wherein the retinol is selected from the group consisting of pan-RAR antagonist compound VIII, RARα selective antagonist (Compound II), and RXR agonist SR11237 and compound V (4-[1-[5,6-Dihydro-3,5,5-trimethyl-8-(1-methylethyl)-2-naphthzenyl]-ethenyl] benzoic acid. The specification further discloses a

method of enhancing antigen presentation of immature antigen presenting cell in vitro comprising contacting said dendritic cell with an effective amount of pan RXR agonist SR11237 and an inflammatory cytokine or a specific RARα antagonist BMS749 and an inflammatory cytokine. The specification also discloses that retinoic acid has been shown to either enhance or decrease immune responses depending on a number of factors such as the type of retinol used, the receptors, i.e., RARα, RARβ, RARγ, pan RAR, RXR, to which it binds, etc. However, the immunomodulating effect depends on the maturity of the dendritic cell as neither mature dendritic cell and monocytes died after exposure to retinoids (See paragraph bridging page 87 and 88). The specification on page 24 discloses that the antigen-presenting cells in the claimed methods may be any antigen-presenting cell, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and the like. The specification on page 29 defines the term "cytokine" as growth factors, interleukins, colony-stimulating factors, interferon and lymphokines, which may be natural, synthetic, or Recombinant, analogues or homologues and TNFα analogues. The specification further defines "antigen-presenting cell" refers to any cell, regardless of the tissue derivation or source of the cell, that is involved in certain aspects of the immune response of an organism... Antigen-presenting cells are any cells capable of carrying out the process of antigen processing and presentation, including but not limited to macrophages (including tissue-fixed macrophages, such as Kupffer cells, histiocytes, etc.), dendritic cells (including immature dendritic cells such as Langerhans cells), monocytes (and monocyte-derived antigen-presenting cells such as monocyte-derived macrophages), certain B cells, certain antigen-presenting epithelial cells, and "the like".

Other than the specific retinoids and the specific inflammatory cytokines for the claimed method, there is insufficient written description about the structure associated with function of *any* "Pan-RXR agonist", *any* "RAR antagonist", *any* "variants", any "derivatives" and "analogues" of TNFα or IL-1β because the term "agonist", "antagonist", "analog", "derivatives" and "compound" could be a polynucleotide, a polypeptide, or a small organic molecule. Even if the method is limited to the specific retinoids and the specific cytokine, the method of modulating the immune system of an animal by affecting the "physiology" of *any* antigen-presenting cell such as mature APC, macrophage, monocytes, Kupffer cells, and histiocytes, is not adequately

described because the specification discloses that the immunomodulating effect of the specific retinoid and TNF alpha is limited to immature dendritic cells. Further, the specification discloses only a method for the inducing apoptosis and antigen presentation of immature dendritic cells *in vitro*, the claimed method of modulating the immune system of an animal wherein modulating can be inhibitory or stimulating by affecting any physiology of any antigen-presenting cell in said animal is not adequately described. Given the lack of additional representative species of antigen presenting cell, and the combination of various retinoids and various cytokines for the claimed method, one of skill in the art would conclude that Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 5 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "salts, esters and prodrugs thereof" in claim 5 is indefinite and ambiguous because "SR11237" is a singular compound. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. It is suggested that the claim be amended to recite "salt, ester and prodrug thereof".

The "active fragments, variants, analogues, and derivatives thereof" in claim 10 is indefinite and ambiguous because "TNFα, IL-1β" as written is a singular compound. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. It is suggested that the claim be amended to recite "active fragment, variant, analogue, and derivative thereof"

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Trinchieri *et al* (Blood 69(4): 1218-24, April 1987; PTO 892).

Trinchieri *et al* teach a method of modulating the immune system of an animal by affecting the physiology such as differentiation of undifferentiated promyelocytic HL60 (non-adherence) to differentiated (adherent) monocyte and/macrophage phenotype (antigen presenting cells) with a retinoid such as retinoic acid and a cytokine such as tumor necrosis factor (TNFα) (See abstract, in particular). The reference monocyte and/macrophage cell is an antigen presenting cell as defined on page 29 of instant specification. Trinchieri *et al* teach that the combination of tumor necrosis factor (TNFα) and retinoic acid is useful for inducing differentiation and growth inhibition of human promyelocytic leukemia (See Discussion, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Mehta *et al* (J Leukoc Biol 55(3): 336-42, March 1994; PTO 892).

Mahta *et al* teach a method modulating the immune system by affecting the physiology such as nitric oxide production of antigen presenting cell such as macrophage or macrophage cell line such as RAW 264.7. The reference method comprises contacting the reference antigen presenting cell such as murine peritoneal macrophage or macrophage cell line such as RAW 264.7 with a retinoid such as all-trans-retinoic acid (RA) and a cytokine such as interferon gamma that inhibits the activation of macrophage (See abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta *et al* (J Leukoc Biol 55(3): 336-42, March 1994; PTO 892) in view of Zhou *et al* (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892).

Mahta *et al* teach a method modulating the immune system by affecting the physiology such as nitric oxide production of antigen presenting cell such as macrophage or macrophage cell line such as RAW 264.7. The reference method comprises contacting the reference antigen presenting cell such as murine peritoneal macrophage or macrophage cell line such as RAW 264.7 with a retinoid such as all-trans-retinoic acid (RA) and a cytokine such as interferon gamma that inhibits the activation of macrophage (See abstract, in particular).

The claimed invention in claim 10 differs from the teachings of the reference only that the method wherein the cytokine is TNFα.

Zhou *et al* teach that dendritic cells such as monocytes derived dendritic cell or Langerhans cell in the epidermis of the skin are the most potent antigen-presenting cells (See page 2588, column 1, in particular). Zhou et al further teach that cytokine treatment such as GM-CSF, IL4 and TNF induces monocyte derived dendritic cell differentiation such as CD83+ dendritic cell morphology, increase antigen presentation to T cell as measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the interferon gamma in the method of modulating immune system of an animal as taught by Mahta *et al* for the various cytokine such as TNF alpha as taught by Zhou et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zhou *et al* teach that dendritic cells such as monocytes derived dendritic cell or Langerhans cell in the epidermis of the skin are the most potent antigen-presenting cells (See page 2588, column 1, in particular) and these cells have potential implications for the development of therapeutic agents for use in allergy, autoimmunity and transplantation (See abstract, in particular).

18. Claims 1-2, and 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta *et al* (J Leukoc Biol 55(3): 336-42, March 1994; PTO 892) in view of US Pat 5,552,271 (Sept 1996, PTO 1449).

The teachings of Mahta et al have been discussed supra.

The claimed invention in claim 4 differs from the teachings of the reference only that the method wherein the retinoid is a pan-RSR agonist and an RAR antagonist.

The claimed invention in claim 5 differs from the teachings of the reference only that the method wherein the pan-RXR agonist is SR11237 and pharmaceutically acceptable salts, esters and prodrugs thereof.

The '271 patent teaches a method of inhibiting an activity of a retinoid X receptor heterodimer formation using a pan-RXR agonist such as SR11237 (See entire document, abstract, column 12, line 20-35, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the retinoid in the method of modulating immune system of an animal as taught by Mahta *et al* for the various retinoid such as pan-RXR agonist is SR11237 as taught by the '271 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '271 patent teaches that pan-RXR agonist such as SR11237 is useful as a method of inhibiting an activity of a retinoid X receptor heterodimer formation (See entire document, abstract, column 12, line 20-35, in particular). Mahta *et al* teach that retinoid such as all-trans-retinoic acid (RA) in combination with an cytokine such as interferon gamma can modulate the immune system by affecting the physiology of antigen presenting cell such as RAW by inhibiting the activation of macrophage (See abstract, in particular).

19. Claims 1-2, 10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop *et al* (Exp Dermatol 3(5):204-11, Oct 1994; PTO 892) in view of Zhou *et al* (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892) or Hausser *et al* (Immunobiology. 197(5):534-42, Nov 1997; PTO 892) or Cumberbatch *et al* (Arch Dermatol Res. 289(5):277-84, Apr 1997; PTO 892).

Dunlop *et al* teach a method of modulating the immune system of an animal such as mice by affecting the physiology such as cell maturation and allogeneic cell-stimulating capability of antigen-presenting cell such as Langerhans cell from the skin by administering a retinoid such as all-trans retinoic acid (See abstract, in particular).

The claimed invention in claim 1 differs from the teachings of the reference only that the method comprises contacting said antigen-presenting cell with an effective amount of at least one retinoid and an effective amount of at least one cytokine whereby the physiology of said antigen-presenting cell is affected.

The claimed invention in claim 10 differs from the teachings of the reference only that the method wherein the cytokine is TNFα or IL-1 beta.

Zhou *et al* teach that dendritic cells such as monocytes derived dendritic cell or Langerhans cell in the epidermis of the skin are the most potent antigen-presenting cells (See page 2588, column 1, in particular). Zhou *et al* further teach that cytokine treatment such as GM-CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular).

Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular).

Cumberbatch *et al* teach that intradermal administration of TNF-alpha or IL-1 activate Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. Cumberbatch *et al* further teach that both IL-1 beta and TNF-alpha can each stimulate the migration of epidermal LC, but that the changes induced by these cytokines are not identical (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modulate the immune system as taught by Dunlop *et al* by including cytokine such as TNF alpha that activates antigen presenting cell as taught by Zhou *et al,*

Hausser *et al* or Cumberbatch *et al* or cytokine such as IL-1 beta as taught by Cumberbatch *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zhou *et al* further teach that cytokine treatment such as GM-CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular). Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular). Cumberbatch *et al* teach that intradermal administration of TNF-alpha or IL-1 activate Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules.

20. Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop *et al* (Exp Dermatol 3(5): 204-11, Oct 1994; PTO 892) in view of Zhou *et al* (Proc. Natl. Acad. Sci USA 93: 2588-2592, March 1996; PTO 892) or Hausser *et al* (Immunobiology. 197(5): 534-42, Nov 1997; PTO 892) or Cumberbatch *et al* (Arch Dermatol Res. 289(5): 277-84, Apr 1997; PTO 892) as applied to claims 1-2, 10 and 16 mentioned above and further in view of US Pat 5,552,271 (Sept 1996, PTO 1449).

The combined teachings of Dunlop *et al*, Zhou *et al*, Hausser *et al* and Cumberbatch *et al* have been discussed supra.

The claimed invention in claim 4 differs from the combined teachings of the references only that the method wherein the retinoid is a pan-RSR agonist and an RAR antagonist.

The claimed invention in claim 5 differs from the combined teachings of the references only that the method wherein the pan-RXR agonist is SR11237 and pharmaceutically acceptable salts, esters and prodrugs thereof.

The '271 patent teaches a method of inhibiting an activity of a retinoid X receptor heterodimer formation using a pan-RXR agonist such as SR11237 (See entire document, abstract, column 12, line 20-35, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the retinoid in the method of modulating immune system of an

animal as taught by Dunlop *et al* for the various retinoid such as pan-RXR agonist is SR11237 as taught by the '271 patent in combination with various cytokine such as TNFα as taught by Zhou *et al,* Hausser *et al*, or Cumberbatch *et al* or IL1β as taught by Cumberbatch *et al* for modulate the immune system by affecting one of the physiology of antigen presenting cells as taught by Dunlop *et al,* Zhou *et al,* Hausser *et al*, and Cumberbatch *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '271 patent teaches that pan-RXR agonist such as SR11237 is useful as a method of inhibiting an activity of a retinoid X receptor heterodimer formation (See entire document, abstract, column 12, line 20-35, in particular). Zhou *et al* further teach that cytokine treatment such as GM-CSF, IL4 or TNFα induces monocyte derived dendritic cell differentiation by acquiring CD83+, dendritic cell morphology, and the capacity of said cell to present antigen to T cell that can be measured by mixed leukocyte reactions (See Figure 4B, page 2591, column 1, in particular). Hausser *et al* teach that treating monocyte derived dendritic cell (mdDC) with TNF or soluble CD40L led to enhanced MHC and accessory surface antigen expression with significantly elevated T cell stimulatory activity (See abstract, in particular). Cumberbatch *et al* teach that intradermal administration of TNF-alpha or caused the activation of Epidermal Langerhans cells (LC), characterized by the acquisition of a more dendritic morphology and the increased expression of Ia molecules. Cumberbatch further teach that both IL-1 beta and TNF-alpha can each stimulate the migration of epidermal LC to site of infection (See abstract, Discussion, in particular).

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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